GRAVES' OPHTHALMOPATHY EVOLUTION STUDIED BY MRI DURING CHILDHOOD AND ADOLESCENCE

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Pediatric patients with Graves' disease (n = 26) were studied longitudinally by magnetic resonance imaging of the orbits, allowing an assessment of the enlargement of the extraocular muscles and orbital volume variations. The positive outcome of Graves' ophthalmopathy correlated with low TRAb (autoantibodies to thyroid-stimulating hormone receptor) titers at diagnosis and during follow-up and with prepubertal condition at diagnosis. ***(J Pediatr 2004;144:527-31)***

Graves' ophthalmopathy (GO) is a complication of Graves' disease characterized by proptosis, caused by the enlargement of the extraocular muscles and augmentation of orbital connective tissue and fat.[1] As opposed to adults, children with Graves' disease rarely have severe infiltrative ophthalmopathy, and exophthalmos is generally mild, nonprogressive, and possibly reversible.[2]

The aim of the current study was to better understand the role of residual pubertal orbital growth in the evolution of GO. To this purpose, we did a longitudinal study on a group of children and adolescents affected by Graves' hyperthyroidism, using magnetic resonance imaging (MRI) of the orbits.

METHODS

Consecutive Italian patients (n = 26, 21 girls) with Graves' disease from the endocrine outpatients of our clinic took part in the study. Informed consent was obtained from the parents of each patient before starting the study, and the local hospital ethics committee approved the study.

At the time of diagnosis, the patients' mean age was 10.15 ± 2.69 years (age range, 4.26-14.65 years); 13 were prepubertal, and 13 showed Tanner stage ≥2.

The diagnosis of Graves' disease was established by the detection of elevated serum-free T3 (FT3) and free T4 (FT4) concentrations and suppressed thyroid-stimulating hormone (TSH) levels, with high serum titers of autoantibodies to TSH receptor (TRAb), typical thyroidal echographic pattern, and high and diffuse ^{99}Tc thyroidal uptake. A goiter was clinically evident at diagnosis in 22 of the 26 patients.

An ophthalmic evaluation was done on all patients at diagnosis, including measurements of proptosis with the use of the Hertel exophthalmometer. A value >20 mm was considered diagnostic of exophthalmus.[1,3] We considered patients to be affected by GO if they had clinical signs of ocular involvement (ie, upper lid retraction, lid lag, or staring eyes) with exophthalmus or MRI signs of muscular enlargement.

MRI of the orbital region was performed shortly after the diagnosis of Graves' disease (mean age, 10.49 ± 2.61 years; range, 4.71-14.81) to discover the presence of alterations in the contents of the orbital tissues. MRI (1.5-T superconductive magnetic unit; Somatom 58, Siemens, Erlangen, Germany) was done with SE T2-weighed transversal scans (TR/TE, 2200/90 ms), using a 5-mm slice thickness, 1-mm distanct factor, subsequently by SE T1-weighed axial and sagittal scans (TR/TE, 550/15 ms), using a 3-mm slice thickness, 0.5-mm distanct factor, and finally by SE T1-weighed fat suppression coronal scan (TR/TE, 650/15 ms). In particular, we evaluated bony orbital volume,[4,5] muscular enlargement,[6] muscular fat infiltration, and increase in orbital fat.

GO	Graves' ophthalmopathy	TRAb	Autoantibodies to thyroid-stimulating hormone receptor
MRI	Magnetic resonance imaging	TSH	Thyroid-stimulating hormone

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Submitted for publication Jan 13, 2003; last revision received Nov 20, 2003; accepted Jan 12, 2004.

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0022–3476/$ - see front matter

10.1016/j.jpeds.2004.01.033

Table. Age, pubertal stage, opthalmologic signs, intraorbital volume, MRI pattern, TRAb levels both at diagnosis (I) and at the end of follow-up (II), and clinical outcome of patients studied

	Age at MRI (y)		Pubertal stage (Tanner)		Proptosis[a] (mm)				Orbital volume (cm^3)[b]			
Patient	I	II	I	II	I R	I L	II R	II L	I R	I L	II R	II L
1	10.5	14.3	Ph2, B2	Ph4, B4	23	21	20	19	24.5	24.4	25.6	25.6
2	6.5	8.6	Ph1, G1	Ph1, G1	22	23	20	20	24.3	24.4	25.3	25.2
10	8.2	16.7	Ph1, B1	Ph5, B5	24	23	20	19	24.3	24.2	25.5	25.5
14	9.9	17.4	Ph1, B1	Ph4, B4	20	22	18	18	24.5	24.7	26.0	26.1
15	6.2	10.7	Ph1, B1	Ph2, B2	20	20	18	18	25.0	25.1	26.0	25.9
24	10.5	14.6	Ph1, B1	Ph4, B4	23	22	20	20	23.0	23.0	24.2	24.1
Group A (n = 6)	**8.7 ± 1.9**	**13.7 ± 3.4**	**5 Prepub 1 Pub**	**1 Prepub 5 Pub**	**22.0 ± 1.7[e]**	**21.8 ± 1.2[e]**	**19.3 ± 1.0**	**19.0 ± 0.9**	**24.2 ± 0.7**	**24.3 ± 0.7**	**25.5 ± 0.7**	**25.4 ± 0.7**
6	12.5	14.7	Ph3, B3	Ph4, B4	20	19	24	23	27.0	26.8	27.4	27.3
8	13.8	21.3	Ph3, B3	Ph5, B5	20	22	20	21	26.5	26.5	27.0	27.0
17	14.3	17.4	Ph4, B4	Ph5, B4	19	19	22	23	26.5	26.5	26.9	27.0
21	11.8	15.3	Ph2, B2	Ph4, B4	22	22	21	20	28.0	28.0	29.1	29.0
26	14.8	19.2	Ph3, G3	Ph5, G5	22	21	21	20	27.8	27.8	28.1	28.2
Group B (n = 5)	**13.4 ± 1.2**	**17.6 ± 2.7**	**5 Pub**	**5 Pub**	**20.6 ± 1.3[h]**	**20.6 ± 1.5[h]**	**21.6 ± 1.5[i]**	**21.4 ± 1.5[i]**	**27.2 ± 0.7**	**27.1 ± 0.7**	**27.7 ± 0.9**	**27.7 ± 0.9**
3	13.6	21.0	Ph3, B3	Ph5, B5	19	19	19	18	25.9	25.8	26.4	26.4
4	4.7	6.9	Ph1, B1	Ph1, B1	17	18	18	18	22.1	22.2	22.7	22.8
5	13.2	15.2	Ph3, B3	Ph4, B5	20	20	19	20	26.8	26.8	27.2	27.3
7	11.5	13.5	Ph2, B2	Ph3, B3	18	18	19	18	24.5	24.5	24.9	24.8
9	10.9	14.6	Ph2, B2	Ph4, B4	18	18	18	18	23.0	23.1	23.8	23.8
11	10.5	13.0	Ph1, B1	Ph2, B3	19	20	19	20	24.7	24.8	25.2	25.3
12	10.1	20.2	Ph1, G1	Ph5, G5	20	20	20	19	25.0	25.0	26.5	26.5
13	13.6	20.2	Ph3, B3	Ph5, B5	18	18	19	18	27.1	27.1	27.6	27.7
16	8.8	12.9	Ph1, G1	Ph2, G2	18	17	18	17	26.0	26.0	27.1	27.1
18	7.5	12.5	Ph1, B1	Ph2, B3	17	17	18	18	24.7	24.7	25.7	25.8
19	11.3	17.6	Ph2, B3	Ph5, B5	20	19	19	18	27.0	26.9	27.7	27.6
20	8.8	14.7	Ph1, B1	Ph3, B4	17	17	19	18	22.0	22.0	23.0	23.0
22	12.7	17.2	Ph2, G2	Ph4, G4	20	20	19	19	28.5	28.5	29.6	29.7
23	7.8	13.8	Ph1, B1	Ph3, B3	19	18	20	20	24.2	24.1	25.5	25.6
25	8.4	15.3	Ph1, B1	Ph3, B4	18	19	19	19	26.0	26.2	27.2	27.3
Group C (n = 15)	**10.2 ± 2.7**	**15.2 ± 4.0**	**8 Prepub 7 Pub**	**1 Prepub 14 Pub**	**18.5 ± 1.1**	**18.5 ± 1.1**	**18.8 ± 0.7**	**18.5 ± 0.9**	**25.2 ± 2.0**	**25.3 ± 1,9**	**26.0 ± 2.1**	**26.1 ± 2.0**

Group A, Patients with ophthalmopathy improvement or regression; group B, patients with ophthalmopathy persistence or worsening; group C, patients without GO. Data are expressed as mean ± SD or median and range (min-max).
[a]Separate value of right (R) and left (L) eyes (in mm) measured by Hertel exophtalmometer.
[b]Separate value of right (R) and left (L) orbital volume (in cm^3).
[c]TRAb U/I (normal values <15 U/I) values are expressed as median and range (min-max).
[d]Outcome of thyroid disease: *MT*, medical therapy; *S*, surgery: near-total thyroidectomy; *CR*, complete remission.
[e]$P < .0001$ vs group C.
[f]$P < .05$ vs group C and ($P < .001$) vs group B.
[g]$P < .05$ vs group C.
[h]$P < .01$ vs group C.
[i]$P < .001$ vs group C.
[j]$P < .001$ vs group C.
[k]$P < .01$ vs group C and ($P < .05$) vs group A.
Red, reduced; *Prepub*, prepubertal; *Pub*, pubertal.

In our experience, normal values for orbital volume (cm^3) are as follows: female subjects: 22.6 ± 3.1 (5-10 years), 25.5 ± 2.8 (11-15 years), and 26.1 ± 2.5 (16-20 years); male subjects: 23.8 ± 3.3 (5-11 years), 26.3 ± 2.7 (12-16 years), and 27.2 ± 1.8 (17-21 years). Patient data referred to this population, and the values were expressed also as SD score (measured value minus mean)/standard deviation.

The medial and lateral rectus muscles were measured on axial scans; the superior rectus and the levator palpebra superior muscles were measured together as a single superior muscle group; diameters of the superior muscle group, the inferior rectus muscle, and the superior oblique muscle were measured on coronal scans.[7] The diameter of each muscle was measured at its maximum. Extraorbital muscles were consid-

Table. continued

	Obital volume (SDs)		Muscular enlargement at MRI		TRAb U/l[c]		
% Δ Orbital Volume	I	II	I	II	I	II	Outcome[d]
4.5	0.6	0.1	+	+ (red)	185	55	S
4.0	0.2	0.4	+	Almost −	102	32	MT
6.0	0.5	−0.2	+ (right ++)	Almost −	405	120	CR
6.0	0.6	0.1	+	+ (red)	73	18	CR
4.0	0.8	1.1	+	−	21	20	MT
5.0	0.1	−0.5	+	+ (red)	160	85	MT
4.9 ± 0.9[f]	**0.4 ± 0.3**	**0.2 ± 0.5**			**131 (21-405)**[g]	**26 (12-85)**	
			−				
1.5	0.5	0.7		+	400	258	S
2.0	0.4	0.4	+	+	82	12	CR
1.5	0.4	0.3	−	+	280	256	S
3.5	0.9	1.3	+	+	260	188	S
1.2	0.6	0.5	+	+	102	10	CR
1.9 ± 0.9	**0.5 ± 0.2**	**0.6 ± 0.4**			**260 (82-400)**[j]	**188 (10-258)**[k]	
2.0	0.1	0.1	−	−	33	25	S
2.5	−0.2	0.0	−	−	41	38	MT
1.5	0.5	0.6	−	−	27	32	MT
1.5	−0.4	−0.2	−	−	110	54	MT
3.5	0.1	−0.6	−	−	55	48	S
2.0	0.7	−0.1	−	−	68	24	MT
6.0	0.4	−0.4	−	−	31	45	S
2.0	0.6	0.6	−	−	28	22	CR
4.0	0.7	0.3	−	−	110	87	MT
4.0	0.7	0.1	−	−	55	18	MT
2.5	0.5	0.6	−	−	38	10	CR
4.5	−0.2	−0.9	−	−	98	16	CR
4.0	0.8	1.4	−	−	68	25	CR
5.5	0.5	0.0	−	−	45	18	CR
4.5	1.1	0.6	−	−	68	75	S
3.3 ± 1.5	**0.4 ± 0.4**	**0.2 ± 0.6**			**55 (27-110)**	**25 (10-87)**	

ered enlarged when diameters were ≥+2 SD of our personal data; specifically, medial rectus ≥4.7 mm, lateral rectus ≥4.6 mm, superior group ≥5.3 mm, inferior rectus ≥5.8 mm, and superior oblique ≥4.0 mm.

A second MRI was performed with the the same MRI apparatus and identical measures used, after a mean period of 4.86 ± 2.28 years (range, 2.02-10.13) and at a mean age of 15.35 ± 3.54 years (range, 6.91-21.27). At this stage, each patient was euthyroid: 9 were in complete remission, 8 were receiving L-thyroxine replacement treatment after near total thyroidectomy, and 9 were receiving combined treatment with L-thyroxine and propylthiouracil. All patients and their parents were non-smokers.

Serum titers of anti-TRAb were measured by radioreceptor assay (TRAK-Assay, BRAHMS Diagnostica GmbH, Berlin, Germany), with the use of the TSH receptor isolated from porcine thyroid; the intra-assay and interassay coefficients of variation were < 7.2% and < 13.2%, respectively. The analytical sensitivity of this assay was 2.4 U/L.

Results are expressed as mean ± SD and as median and range. Statistical analysis was performed with the use of the unpaired Student *t* test, with the Bonferroni correction when appropriate and χ^2 analysis and Mann-Whitney nonparametric test in the case of abnormal distribution. All statistical analyses were performed with the use of a data analysis system (StatView 4.5, Abacus Concepts, Inc, Berkeley, Calif) run on an Apple PowerMac computer. Statistical significance was set at a value of $P < .05$.

RESULTS

The Table shows age, pubertal stage, ophthalmologic signs, intraorbital volume, MRI pattern, and TRAb levels of the patients studied, both at diagnosis and at the end of follow-up. Values of calculated intraorbital volume are reported as absolute numbers (cm^3) and in SD scores compared with the normal data referring to the same age group. Muscular swelling is reported as present (+) or absent if the dimensions of extraocular muscles were or were not greater than the normal limit for our population.

Clinical signs of GO and exophthalmos were evident at the time of diagnosis in 8 of 26 patients. The remaining patients showed no symptoms or signs of ocular involvement at this time. MRI confirmed exophthalmos, when it was clinically present, by a pattern of muscular enlargement, with no muscular fat infiltration or increase in intraorbital adipose tissue. Another patient (No. 15) showed a pattern of muscular enlargement despite the absence of clinical signs of GO. MRI of the orbital region was negative in all the other patients.

During follow-up, another 2 patients (Nos. 6 and 17), both pubertal at diagnosis and in a euthyroid state, showed clinical and MRI patterns of GO 15 and 22 months from diagnosis, respectively. They had had no clinical or MRI signs of GO at diagnosis, although high titers of TRAb were evident at diagnosis and during follow-up.

During follow-up, the patients who had had ocular involvement at diagnosis had almost complete regression of clinical signs and symptoms of GO. The MRI pattern of muscular enlargement showed no variation in 3 patients (Nos. 8, 21, and 26) who were pubertal at diagnosis; discrete regression in 3 patients (Nos. 1, 14, and 24): 2 prepubertal and 1 pubertal at diagnosis; and almost complete regression in 3 patients (Nos. 2, 10, and 15) who were prepubertal at diagnosis.

The increase in orbital volume between the first and second MRI was 3.5% ± 1.5%, but it was more significant in prepubertal rather than in pubertal patients (4.46% ± 1.60% vs 2.50% ± 1.18%; $P < .01$).

Hyperthyroid patients with GO at diagnosis and during follow-up had significantly higher anti-TRAb titers than those without GO (mean ± SD: 188.2 ± 131.7 vs 58.3 ± 28.5 U/L; $P < .05$; median (range, minimum to maximum): 160 (21 to 405) vs 55 (27 to 110) U/L). The 95% upper-level confidence interval between groups was 201.7 U/L, so we took this value as a cutoff for higher risk of GO. There were no significant differences in other measures studied (age at diagnosis, orbital volume, FT3, FT4, TSH, anti-thyroglobulin antibody, and anti-thyroid peroxidase antibody levels, data not shown) among groups matched for sex, pubertal stage, and therapeutic options during follow-up.

We subdivided all the patients showing clinical or MRI signs of GO at diagnosis and during follow-up (11 total) into 2 groups, based on the evolution of GO: 6 patients had an improvement or regression of ophthalmopathy (group A), whereas 5 showed persistence or worsening of the ophthalmopathy (group B).

The Table shows these 2 groups of patients compared with hyperthyroid patients without GO (group C). At diagnosis, 5 of the 6 patients in group A were prepubertal, whereas all 5 patients in group B were pubertal; the difference was statistically significant by χ^2 analysis ($P < .01$). The patients in group A had an increase in orbital volume that was significantly higher than that of the children in group B (4.91% ± 0.91% vs 1.94% ± 0.92%; $P < .001$) and statistically different from that of group C.

TRAb levels of the patients in group B were significantly higher at the end of follow-up than both those of the patients in group A ($P < .05$) and group C ($P < .01$).

DISCUSSION

Graves' ophthalmopathy is less common in children than in adults. Orbital signs and symptoms occur in approximately one half of hyperthyroid children, and exophthalmos, when present, is usually mild.[2] The cause of this different behavior of GO in hyperthyroid children and adults is not clearly understood.

Because our patients with GO had significantly higher TRAb titers than those without ophthalmopathy, elevated TRAb titers at diagnosis[6] and especially during follow-up were associated with an elevated risk of persisting GO or its onset during follow-up. In particular, patients with TRAb levels >200 U/L have an increased risk for GO. On the contrary, the patients with better progression of GO had low TRAb titers.

In our pediatric patients with GO, MRI showed only the enlargement of the extraocular muscles. This finding is typical of the active, edematous stage of the eye disease in children and adolescents, in which the fibrotic stage is uncommon. Moreover, MRI confirmed regression of the ophthalmopathy in the 6 patients in group A, already clinically evidenced.

During follow-up, the prepubertal patients who had a tendency to GO regression also showed an increse of orbital volume. Probably during pubertal development, the residual orbital growth could create a physiologic decompression with a positive effect on the evolution of GO.

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50 Years Ago in *The Journal of Pediatrics*

A ROCKING BED RESPIRATOR FOR USE WITH PREMATURE INFANTS IN INCUBATORS

Lee HF. J Pediatr 1954;44:570-3

Premature infants born 50 years ago faced an enormous, uphill battle for survival. Such fundamental treatments such as mechanical ventilation, antibiotics, and appropriate feeding formulations were not in widespread use. For those born close enough to term to avoid some of the most devastating conditions, common problems like the apnea of prematurity still posed a challenge.

Physicians treating respiratory ailments in adults with normal lung compliance (eg, polio victims) had demonstrated that a rocking bed would enhance diaphragmatic excursion and promote gas exchange. In this paper, Dr Lee described the development of a similar technology, adapted for use inside an incubator, and proposed that it might prove helpful in the management of infants with prolonged apnea. Challenges in the development of this design included the size restrictions of an incubator and the need to avoid any electrical equipment in the oxygen-rich environment.

No data were offered to demonstrate that this technology was effective, but it is not difficult to imagine that the repeated stimulation of the rocking bed would be effective in arousing a moderately premature infant to breathe. Subsequent crossover studies of kinesthetic stimulation did not demonstrate a substantial reduction in infant apneas, and, in other studies, theophylline was shown to be superior.[1]

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YMPD774
10.1016/j.jpeds.2004.02.003

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